# Import of Human Drugs and Human Drug Components

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June 2011

# Overview

- **Who are we and what do we do?**
- **Definitions**
- **Recognize various drug import requirements:**
  - **Marketing requirements for Rx and OTC Drugs**
  - **Labeling**
  - **Misbranding & Adequate Directions for Use**
  - **Importation of Finished Drugs and Active Pharmaceutical Ingredients (APIs)**
  - **Registration and Listing Requirements**
  - **Adulteration**

# Import Operations Branch (IOB)

- Created on June 6, 2011 when the CDER Office of Compliance was reorganized. The IOB:
- Serves as an FDA focal point for compliance issues related to imported and exported human drugs.
- Consults with and provides guidance to FDA field offices and consults with the field on import and export issues for specific drug products.
- Coordinates with the Office of Regulatory Affairs (ORA) on policies, programs and procedures related to field operation needs.
- Reviews requests, and issues, when appropriate, export certificates.
- Develops and provides guidance on human drug import and export policies and procedures.

# Human Drug Imports - Compliance

# Drug Imports – Quiz

Q: When does the import process begin?

A. before regulated products leave the exporting country

B. once products reach a CBP point of entry

C. after FDA conducts foreign inspections

D. as soon as the shipment enters US territory

# Definitions

# What is a drug?
# Definition: "Drug" *[FDCA 201(g)(1)]*

Drug is an article …

- Intended to diagnose, cure, mitigate, treat or prevent disease in man or other animals
- Intended to affect the structure or any function of the body of man or other animals (other than food)
- Recognized in the USP/NF, HPUS or any supplement to them
- Intended for use as a component of a drug

# Is it a Drug?

- Regulation 21 CFR 201.128, defines the term “intended uses”
  - Intent is determined by labeling, advertising matter, oral or written statements

- Finished products, active pharmaceutical ingredients (APIs), excipients, and labels/labeling for such products are defined to be drugs. Chemicals can be drugs, but not all chemicals are drugs

- GHB, GBL, DMSO, are chemicals but can also be drugs

# Is it a new drug?
# Definition: "New" drug *[FFDCA 201(p)]*

- "any drug ... the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience..., as safe and effective (GRAS/E) for use under the conditions prescribed, recommended or suggested in the labeling"
- A "new drug" must be covered by an approved new drug application or abbreviated new drug application (NDA/ANDA) to be legally marketed in the U.S. or by an investigational new drug application (IND) *[FFDCA Section 505]*
- Rx and Over-the-Counter (OTC) drugs can both be new drugs

# Is it an OTC or Rx drug?
# Rx Drug - *[FFDCA 503(b)(1)]*

Drugs that cannot be used safely without medical supervision.

- Examples?
  - Injectable* drugs or
  - Drugs to treat serious conditions like heart disease, cancer, or fertility problems

*Generally, injectable drugs are Rx, but insulin is not Rx in every state.

# Is it an Over-The-Counter (OTC) drug?

- A drug for which adequate directions for use can be written (Section 502(f)(1) of the FFDCA and Regulation 21 CFR 201.5
- Can be used safely without medical supervision

  Examples:
  - Medications for fever such as aspirin and acetaminophen
  - Some preparations for common cold or allergies
  - Antacids
  - Some first aid antibiotics

# OTC Drugs

- Most OTC drugs are not covered by NDAs
- Large number of OTC drugs on the market in 1972 did not have FDA approval
- Agency decided to have a class-by-class review for OTC drugs instead of NDAs
- Final rules (OTC monographs) in effect 21 CFR Parts 331 through 358
- Negative monographs at 21 CFR 310
  - Timed-release drugs require new drug application approval (see 21 CFR 310.502(a)(14))

# Drug or Dietary Supplement?

- A dietary supplement (DS) must meet definition of DS found at FDCA Section 201(ff)(1)
- Cannot be a dietary supplement if it is not ingested, or when it is intended to treat, cure, prevent, or mitigate disease
- Products that otherwise can be dietary supplements are drugs if they contain an ingredient such as sildenafil, the active ingredient in Viagra

# Drug or Cosmetic?

- A cosmetic (Section 201(i)) is for cleansing, beautifying, promoting attractiveness, or altering the appearance.

- However, a “cosmetic” with anti-aging claims is a drug.

- Antimicrobial soap and antiperspirant/deodorant products are both drugs and cosmetics.
  - These products must meet both the drug and cosmetic regulations.

# Drug Imports – What rules apply?

# Drug Imports

- 80% of APIs & 40% of finished drugs are imported.
- FDA is responsible for assuring the safety and effectiveness of domestic and imported drugs and other products. Other agencies such as CBP, DEA, and USDA also have responsibility.
- Food, Drug, and Cosmetic Act (FDCA) Section 301 prohibits the interstate shipment (includes importation) of misbranded, adulterated, and unapproved new drugs.

# Entry Review Decisions

Five decisions may result from the entry evaluation process:

(1) Product may proceed – cleared to enter US

(2) Imports office requests additional information for further evaluation e.g. labeling, formulation, Certificate of Analysis (COA)

(3) Information referred to District Compliance Officer for detention consideration

(4) Field examination of product

(5) Product sample collection.

Do not attempt to import drugs without first doing due diligence.

# Imports Compliance – Detention

- Products are detained:
  - because they appear to be unapproved new drugs
  - appear to be misbranded
  - firm is not registered
  - product is not listed
  - for other causes (product appears to be adulterated).
  - Product is an Rx drug that was exported (PDMA)

# Imports Compliance – Detention continued

FDA field offices have the authority to detain drugs that appear to be violative. The detention and Hearing Process happens at the District level – **Work with the district office.** They will contact CDER if warranted.

- Notice of FDA Action – You are notified by the district
- Submit FDA Form 766 and attempt to bring misbranded drugs into compliance
- Pending decision as to the admission of an article, delivery of such article to the owner or consignee may be authorized.
- Unapproved new drugs may not be brought into compliance: RPM Chapter 9 -- *"Do not permit the relabeling of a drug detained on a new drug charge as a means to bring the item into compliance."*

# Imported Drugs - Refusal

Under section 801(a) of the Act, an article (drug) is subject to refusal if it appears from examination or otherwise:

- It has been manufactured, processed, or packed under unsanitary conditions (501(a)(2)(B))
- Forbidden or restricted for sale in the country in which it was produced/exported
- Is adulterated, misbranded, or in violation of section 505 of the Act

# Imports Compliance –Refusal

- Products not brought into compliance are refused admission into the U.S.

- Refused articles must either be destroyed or exported

# New Drug Approval

# New Drug Approval Process
# NDA and ANDA

- Is product specific
- Firm submits data from adequate and well controlled studies on the safety and efficacy of a specific drug
- FDA evaluates data, approves or does not approve the drug
- Every firm must seek FDA approval for any drug product requiring NDA approval

# Marketing Requirements (NDA/ANDA)

An approved new drug must be:

1. Manufactured, packaged, or labeled at a facility covered in the application using the formulation and process approved

2. Manufactured using an Active Pharmaceutical Ingredient (API) supplied by a manufacturer covered in the NDA

# OTC Drug Marketing

- Where there is a final monograph, an OTC drug must meet the final monograph including labeling and formulation.
- Drug must be manufactured under current Good Manufacturing Practices (cGMPs).
- Some drugs switched from Rx to OTC still require NDA (ibuprofen, Advil).
- Bears tamper-evident packaging & labeling (TRP) 21 CFR 211.132
- OTC drug products must also comply with all other FFDCA labeling requirements including drug facts (21 CFR 201.66).

# Drug Label Requirements

All drug labels must bear:

- 502(b) – The name & place of manufacturer, packer, or distributor (also see 21 CFR 201.1)
- 502(b)(2) – Accurate statement of the quantity of contents 502(c) – Must be understandable, must be in English (also see 21 CFR 201.15)
- 502(e) – Established name and quantity of each active ingredient (also see 21 CFR 201.10)

# Drug Label Requirements - Summary

- 502(f)(1) – Adequate directions for use unless exempt (21 CFR 201.5)
- Finished dosage form Rx drugs are exempt if they meet all conditions in 21 CFR 201.100
- 502(f)(2) – Warnings against unsafe use
- 21 CFR 201.17 & 211.137 – Expiration dates
- 21 CFR 201.18 – Lot number

# Questions?

# Misbranding Provisions

# Adequate Directions for Use - Misbranding *[502(f)(1) & 21 CFR 201.5]*

- Definition: “directions under which a layman can use the drug safely and for the purposes for which it is intended”
- 21 CFR 201.128 defines “intended uses”, includes objective intent determined by the expression or circumstances surrounding distribution
- All drugs (including APIs) must bear “adequate directions for use” or meet one of the **exemptions** (If not, then misbranded *[502(f)(1)]*)
- **OTC** finished drug products meet this requirement if they meet a final OTC monograph
- Rx drugs meet this requirement if they meet all conditions set forth in 21 CFR 201.100

# Active Pharmaceutical Ingredient (API)

- What is it?
- What are the regulations for their legal importation?
- How should an API be labeled?
- Should it be listed, and its manufacturer be registered?

# Active Pharmaceutical Ingredient (API) *[21 CFR 207.3(a)(4)] a.k.a. bulk drug substance*

"any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, **becomes an active ingredient or a finished dosage form of the drug…**"

"term does not include intermediates used in the synthesis of such substance"

- Lyophilized drugs such as hGH and hCG are finished drugs, not APIs – Require NDA approval

# Adequate Directions for Use – Definition

- Section 502(f)(1) of the FFDCA states that a drug is deemed to be misbranded unless its labeling bears adequate directions for use.

- Regulation 21 CFR 201.5 defines the term "adequate directions for use" to mean directions under which the layman can use a drug safely and for the purposes for which it is intended.

# Adequate Directions for Use Exemptions from *[502(f)(1) & 21 CFR 201.5]*

- *21 CFR 201.122(a):* API intended for use in a product **approved** in NDA, ANDA, or supplement
- *21 CFR 201.122(b):* API intended for use in product **subject** to an Investigational New Drug (IND)
- *201.122(c):* API intended for use in product subject to a **pending/near** NDA or ANDA or supplement approval
- *21 CFR 201.125:* API intended for use in **teaching, law enforcement, research, and analysis and not for use in humans**
- *21 CFR 312.160:* Finished drug intended for **IND use** in laboratory research animals or in-vitro testing

# Exemptions from Adequate Directions for APIs *[21 CFR 201.122(a)]*

- Intended for use in a product which has an **approved** NDA or ANDA
- Is manufactured by the supplier **approved** in the new drug application
- Is intended for use in **approved** prescription (Rx) and/or over-the-counter (OTC) drugs

# API Exemptions *[21 CFR 201.122(a)]*- *continued*

Labeling bears the statement:

- "Caution: for manufacturing, processing, or repacking"

- "Rx only" - when most dosage forms in which the API may be used are subject to prescription *[503(b)(1)]*

- Meets 21 CFR 201.1 and other labeling requirements

# API Exemptions *[21 CFR 201.122(a)]* - *continued*

## Useful Information submitted to district:

- API product name and NDC number
- Name and address of the API manufacturer
- Number of approved NDA/ANDA or supplement
- Finished dosage drug product name and NDC number

# API for Use in Clinical Studies (a.k.a. IND) *[21 CFR 201.122(b)]*

- Must be covered by an active IND
- Must be going to person(s) authorized in IND
- Meets 21 CFR 201.1 and other labeling requirements
- Labeling must bear:

  "Caution: for manufacturing, processing, or repacking in the preparation of a new drug or new animal drug limited by federal law to investigational use"

# API for Use in Clinical Studies (a.k.a. IND) *[21 CFR 201.122(b)]* - *continued*

## Useful Information:

- IND number
- Sponsor's name and address
- Name of the product

# API for Pending/Near NDA/ANDA (Rx & OTC) *[21 CFR 201.122(c)]*

- Is intended for use in a product subject to a **pending/near** NDA, ANDA, or supplement approval
- Is manufactured by the supplier included in **pending/near** NDA, ANDA, or supplement approval
- Applies to both prescription (Rx) and over-the-counter (OTC) drugs

# API for Pending/Near NDA/ANDA (Rx & OTC) *[21 CFR 201.122(c)]* - *continued*

Labeling (Must):

- Meet 21 CFR 201.1 and other labeling requirements
- Bear "Caution: for manufacturing, processing, or repacking"
- Bear "Rx only"- when most dosage forms in which the API may be used are subject to prescription *[503(b)(1)]*

# API for Pending/Near NDA/ANDA (Rx & OTC) *[21 CFR 201.122(c)]*- *continued*

## Useful Information:

- API product name and NDC number
- Name and address of the API manufacturer
- Pending NDA/ANDA number or supplement
- Finished dosage drug product name and NDC number (if applicable)
- Written commitment that products manufactured with API will not be introduced in commercial distribution until approved

# API for Pending/Near NDA/ANDA (Rx & OTC) Summary *[21 CFR 201.122(c)]-* *continued*

- API must be labeled as per *21 CFR 201.122*
- Finished product must be covered by a pending application or supplement
- API must be from a supplier in the pending application/supplement

# APIs to Manufacture Drugs for Which an NDA Was Submitted [21 CFR 201.122(c)]

NDA has been submitted by has not yet been approved or disapproved.

Application to Manufacture Pre-Submission Batches

- Drug used to conduct the studies needed to generate data required to submit an application or supplement
- FDA may exercise enforcement discretion

Useful Information:

- Explanation that API is intended to generate data to submit an application/supplement
  - Example: Bioequivalence and/or bioavailability batches.
  - Written commitment that product manufactured with API will not be introduced in commercial distribution until approved

# APIs for Pre-Submission Batches [21 CFR 201.122(c)]

## Useful Information – Cont.:

- API product name and NDC #
- Name and address of the API manufacturer
- Name and address of U.S. consignee
- Product must be labeled as per *21 CFR 201.122*
- For NDA supplements - may include NDA/ANDA number to be supplemented and NDC # of finished product

# Drugs for teaching, law, research enforcement & analysis *[21 CFR 201.125]*

- Includes Rx and OTC drug products
- Drug is shipped to persons regularly and lawfully engaged in instruction in pharmacy, chemistry, or medicine not involving clinical use, or engaged in law enforcement, or research not involving clinical use, or in chemical analysis, or physical testing, and is to be used only for such purposes.
- Product name and NDC number
- Name and address of the drug manufacturer
- Name and address of U.S. Consignee
- Written commitment that the quantity offered for import is reasonable for the contemplated research, teaching, analysis, etc.

# Drugs for IND Studies (laboratory animals/in-vitro tests) *[21 CFR 312.160]*

- To conduct R&D work prior to the submission of an IND in animal studies or in-vitro testing
- Must comply with all the requirements under *21 CFR 312.160. Includes only finished drug products, not APIs.*
- *Records must be kept for a period of two years.*
- *Cannot be used in humans.*

# Drugs for IND Studies (laboratory animals/in-vitro tests) *[21 CFR 312.160]* - *continued*

- Labeling (Must): "Caution: Contains a new drug for investigational use only in laboratory research animals, or for tests in-vitro. Not for use in humans"
- Shipper must use due diligence (21 CFR 312.160(a)(2))
- Adequate records must be maintained:
  - Label content demonstrating compliance with *21 CFR 312.160*

# Import Requirements of Investigational New Drugs (INDs)

- Imported drug complies with 21 CFR 312.110(a) and is subject to an IND under 21 CFR 312.40.
- Labeling complies with 21 CFR 312.6

# API - Rx drugs not currently subject to application requirements

- Labeling (Must State):
  - "Caution: For manufacturing, processing, or repacking"
  - "Rx only"
- Examples: Animal/Clinical Studies or Bioequivalence Study
- Useful Information:
  - Name and NDC # of product to be manufactured with the API
  - A statement justifying why an approval is not required for the finished drug product
  - API label content demonstrating compliance with *21 CFR 201.122*

# API for OTC Drugs: Pending & Final Monographs

Labeling (Must State):

- "Caution: for manufacturing, processing, or repacking"
- Useful Information:
  - Name and NDC # of product to be manufactured with the API
  - A statement justifying why an approval is not required for the finished drug product
  - API label content demonstrating compliance with *21 CFR 201.122*

# Registration and Listing

# Registration: Domestic & Foreign

- FDCA 510(b), (i) – Registration Requirements
  - Manufacturers: APIs & finished drug products
  - Repackers and relabelers
  - Control laboratories: registration only
  - Domestic manufactures that pack/repack, label/relabel, etc. drugs under the Import for Export (IFE) requirements

- NO ESTABLISHMENT REGISTRATION?
  - Drug is misbranded under FDCA 502(o) if manufactured in U.S.
  - Drug is misbranded under FDCA 801(o) if foreign manufacturer is not registered and the drug is offered for import
  - Products from foreign firms that are not registered may be refused admission under section 801(o) because the drug listing is inadequate

# Drug Registration & Listing Requirements [FFDCA Sec. 510 & 21 CFR 207]

All foreign firms that manufacture, prepare, propagate, compound, or process a drug imported or offered for import into the U.S. shall, through electronic means …

- Register the name and place of business
- Designate a U.S. Agent
- Provide names of each known importer & person who imports or offers for import
- List all drug products imported or offered for import into the U.S.

# Drug Listing: Requirements

- FDCA 510(j) – Drug Listing

- NO DRUG LISTING or INADEQUATE LISTING?
  - Drug is misbranded under 502(o) and may be refused admission under section 801(a)(3).
- NDC Numbers
  - FDA requests but does not require NDC appear on the product label or labeling
  - If NDC appears on the label it must comply with regulation at 21 CFR 207.35 (b)(3)

# Registration & Listing

- Listed products: assigned National Drug Code number (NDC #)
- NDC # format identifies the following:
  - Manufacturer or distributor
  - Drug
  - Trade package size and type
- Registration & Listing does not indicate FDA's approval of firm or products [21 CFR 207.39]

# Registration: Exemptions

- Pharmacies that operate under applicable local laws that do not manufacture or process drugs for sale (21 CFR 207.10(a))
- Hospitals, clinics, and public health agencies that operate with any applicable laws regulating the practice of medicine and pharmacy (21 CFR 207.10(b))
- Practitioners who are licensed by law to prescribe or administer drugs (21 CFR 207.10(c))
- Persons who manufacture or process drugs not for sale but solely for use in research, teaching, or chemical analysis (21 CFR 207.10(d))
- Manufacturers of harmless inactive ingredients (21 CFR 207.10(e))

# Listing: Exemptions

- Component of a drug (e.g. ingredients or non-API intermediates used to synthesize APIs)
- Drugs not for importation into U.S. (FTZ)
  - Component used to manufacture per 801(d)(1)
- Investigational New Drug (IND) [21 CFR 312]
- Research for own study only and not for research in humans. Not exempt when the importer is different from the researcher.

# Pre-Launch Activities Importation Requests (PLAIR)

Email CDER-OC-PLAIR@fda.hhs.gov to request information.

# Import for Export (IFE) [801(d)(3)]

- Section 322 of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Public Law 107-188

- Signed into law on June 12, 2002, and amended section 801(d)(3) of the FDCA.

- Allows importation of violative articles of drug, i.e., misbranded, adulterated, and unapproved, if the importer provides certain information to FDA at the time of the initial importation into the United States.

# Import for Export (IFE) [801(d)(3)] - continued

- Provided importer affirms in writing that imported drugs will be further processed into products to be exported by the initial owner or consignee in accordance with section 801(e) or section 802 of the Act

- FDA must be provided with certain information:
  - Written statement article (finished dosage form or API) is to be further processed, and the resultant manufacture, processor, packer, distributor or any entity that had possession of the article
  - COA to identify the article
  - Records when requested

# Import for Export (IFE) [801(d)(3)] - continued

- Must execute a bond for any liquidated damages
- Must maintain records of use and/or destruction
- Must destroy any article not used in production

- Article can be refused admission if credible evidence that it is not intended to be further processed
- Prohibited Acts [301(w)]:
  - False information and statement
  - Introduction into interstate commerce any article (including finished)
  - Not submitting and maintaining records and COA

# Transport and Exportation (T&E)

- Products are transported through the U.S. to be exported.

- CBP regulation 19 CFR 18.10, "Kinds of Entry", lists the various entries and withdrawals that may be made for merchandise transported in bond. One kind of entry is the transportation and exportation (T&E) entry. A T&E filed with CBP, allows a party to transport merchandise in bond through the U.S. and export the merchandise intact to a foreign destination without the payment of duties. (See 19 U.S.C. 1553, 19 CFR 18.11, and 19 CFR 18.20.)

# T&E - Continuation

- Possible weaknesses in T&E. Product is not re-exported.
- Large shipment of “Cosmetics” from Saudi Arabia to JFK to Miami to be exported to Haiti
- No documentation that a previous large shipment was exported.
- Customs found the second shipment contained Rx steroids
- Products were seized

# Import Into Foreign Trade Zone (FTZ)

- FTZ is CBP's designation to exempt from payment of duties, taxes, bonds. CBP considers FTZs to be outside of U.S.
- Articles not offered for consumption, thus not considered "imported or offered for import".
- If the FTZis located in the U.S., subject to FDA laws since considered within the "territory" of the U.S.
- 801 does not apply until article is out of FTZ
- Introducing unapproved new drugs into FTZ violates new drugs [505(a)] and prohibited [301(d)]
- Can bring into FTZ articles of drug (bulk or finished) pending approval

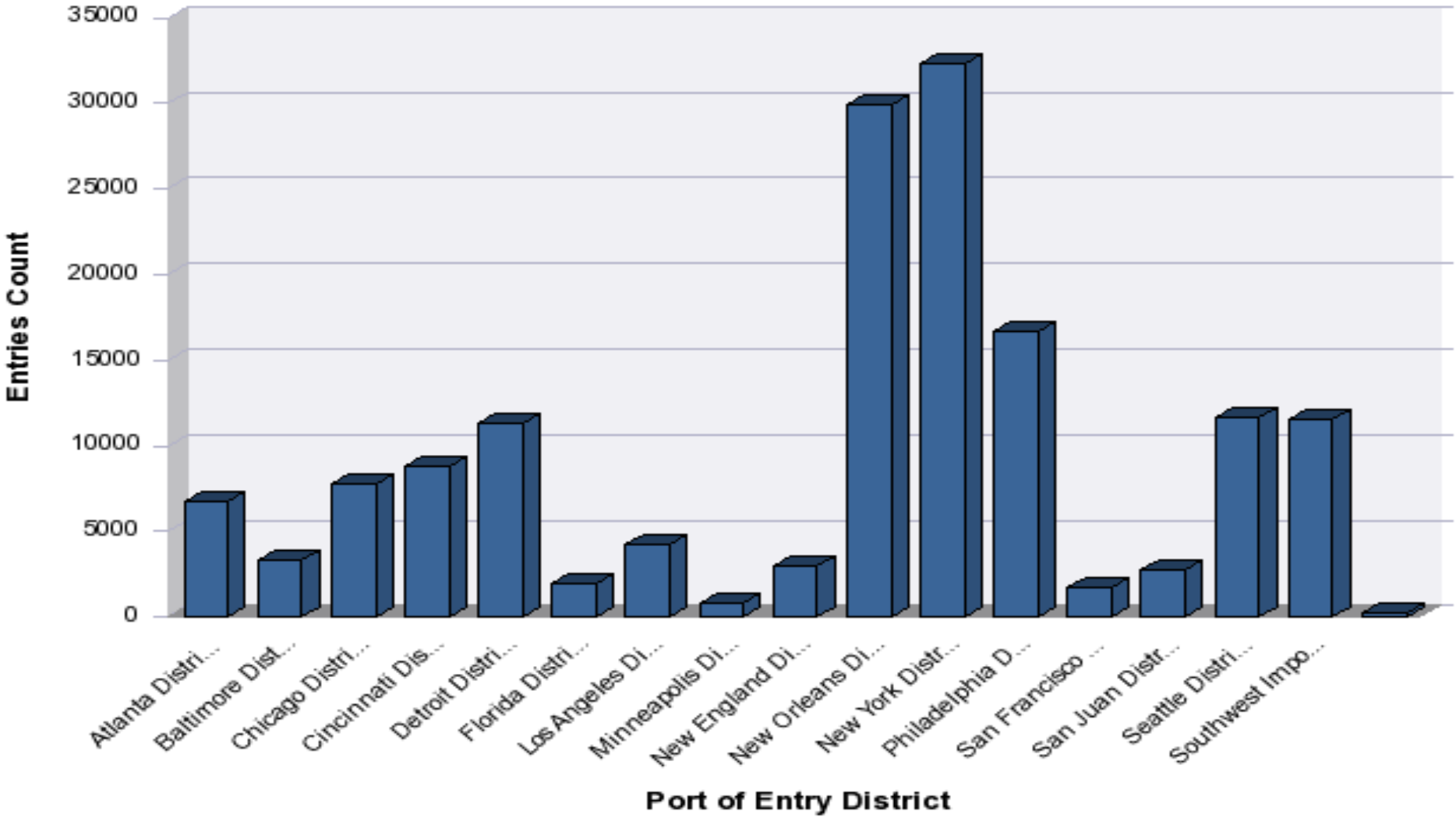
# Secure Supply Chain (SSC)

- Notice (Fed Register 1/15/2009) announcing opportunity for sponsors and foreign manufacturers of APIs & finished drug products
- The SSC program assists the FDA in its efforts to prevent the importation of adulterated, misbranded, or unapproved drugs by allowing the agency to focus its resources on imported drugs that fall outside the program and that may pose such risks.
- Incentive for drug manufacturers to develop secure routes to import APIs and finished drugs, so FDA personnel can focus on drugs imported via less secure supply routes
- Selected participants can import specified finished drug products/APIs with minimal delay at designated ports of entry

# Secure Supply Chain (SSC) continued

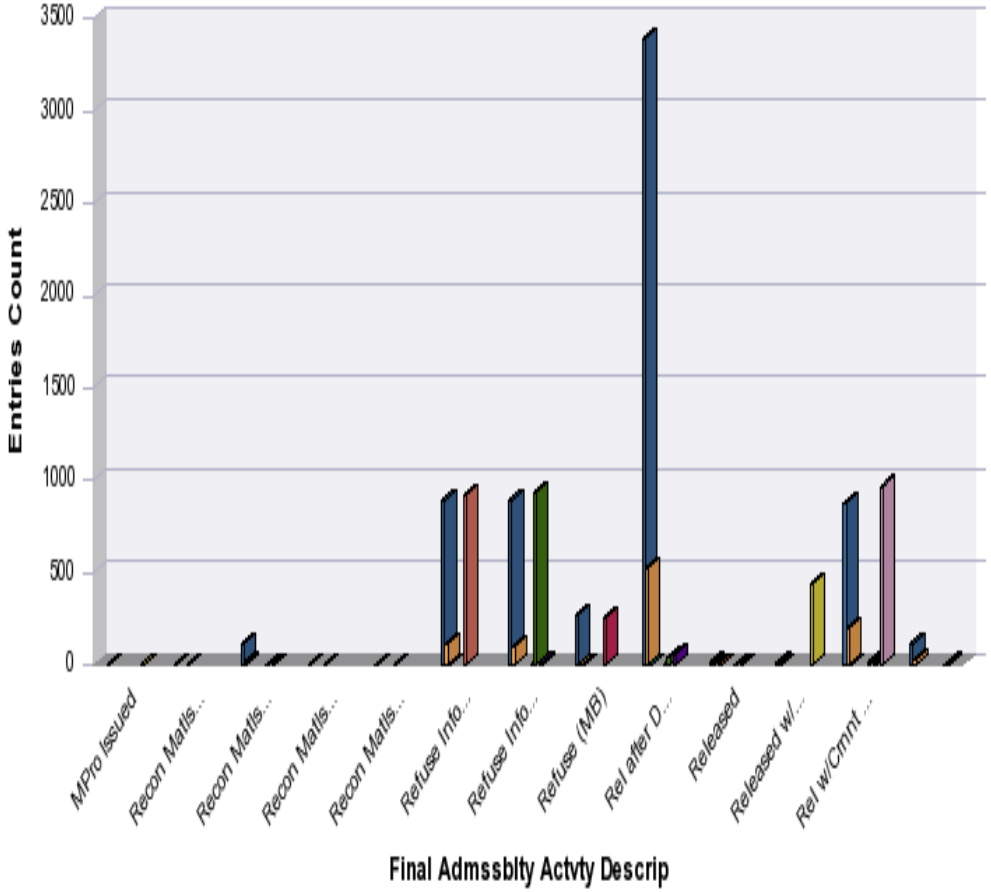
- Selected participants must …
  - Meet all regulatory requirements (cGMP, API, registration, listing, A/NDA applications, etc.);
  - Meet identified minimum criteria;
  - Identify efforts to prevent the importation of diverted and counterfeit drugs.
- Meet CBP Customs-Trade Partnership Against Terrorism (CTPAT) Tier II certified secure supply chain
- SSC to be administered by CDER & DIOP

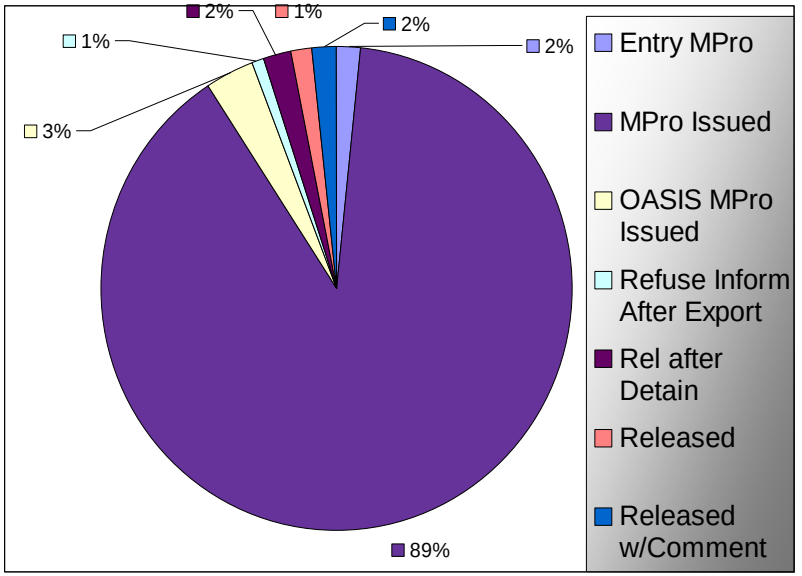
# Drug Imports - 2008



# Drug Imports

## 2008 Imports Outcomes



# DRUG Import Alerts

61-07: Domperidone

62-05: Sterile drugs from facilities not inspected by FDA

66-40: Drugs manufactured in violation of cGMPs

66-41: Unapproved New Drugs

66-57: Unapproved Rx drugs

66-66: Misbranded APIs

66-71: HGH

66-72: Unapproved/misbranded drugs

62-05 Sterile Dosage Form Drugs

# References

- Federal Food, Drug and Cosmetic Act: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/default.htm
- 21 Code of Federal Regulations (CFR): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
- OTC Drug Monographs: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/default.htm
- Regulatory Procedures Manual (RPM) : http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm
- FDA Forms: http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm
- Import Alerts: http://www.accessdata.fda.gov/cms_ia/ialist.html

# Import Operations Branch (IOB) Contact Information

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# Thank you!

Questions?